Multi-Scale Laws of Myocardial Growth and Remodeling

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Introduction

For decades researchers have strived to create realistic computational models to represent the mechanical behavior of the heart [1]. This challenging endeavor faces difficulties in accounting for the complex geometry, fiber structure and material description of the heart. This description depends fundamentally on the underlying microstructure of the heart which is composed of hierarchical fibrous structures. To further complicate modeling efforts, the circulatory system and the cyclical function of the heart need to be numerically reproduced as heart function is critically coupled to the circulatory system and cannot be modeled in isolation.

Here, we propose a method to combine multiple sources of *in vivo* and *ex vivo* data to produce and validate highly realistic subject-specific finite element (FE) models of the porcine heart. This process builds on our previously published research on cardiac modeling [2] by including subject-specific features into almost every aspect of the model to reduce the number of ad hoc modeling assumptions.

By incorporating data from high resolution magnetic resonance imaging (MRI) and diffusion tensor magnetic resonance imaging (DT-MRI), we were able to create high-fidelity representations of the biventricular chambers, myofibers and, for a subject with heart failure (HF), infarcted scar-tissue distribution.

This study introduces the first fully subject-specific cardiac models in healthy and failing states.

Methods

Experimental protocol

Two porcine subjects were used in this study: one normal and one with HF. HF was created by occluding the obtuse marginal branches of the left circumflex artery percutaneously using embolization coils. Ejection fraction declined from 56% at time of occlusion to 32% at time of sacrifice.

Creation of computational heart models

- Geometrically precise fully subject-specific FE models are constructed from high res. *ex vivo* MRI for the geometric reconstruction and DT-MRI for the fiber structure. These models include the full ventricular structure, the endocardial papillary structure and all valve openings: an example is given in Fig. 1.

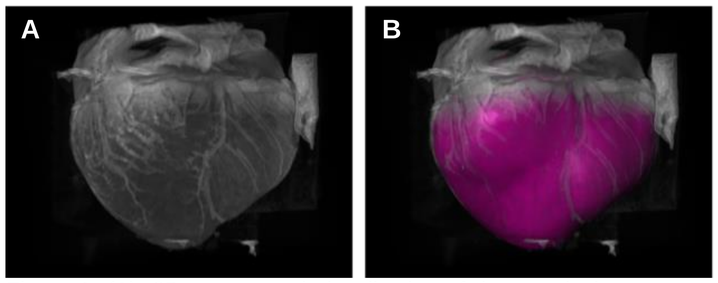

Figure 1: (A): 3D constructed visualization of the ventricular structure from MRI data. (B): The FE geometric segmentation of the ventricular structure over the same background MRI data.

- These models are complemented with constitutive descriptions describing passive and contractile myocardial mechanics which depend on the underlying micro-structure, shown in Fig. 2.

- To simulate closed-loop circulatory flow we couple each model to a lumped Windkessel circulatory flow model (Fig. 2) [2]. This enables closed-loop volume exchange, the modeling of multiple cardiac cycles and realistic cyclical pumping akin to the physiological beating heart.

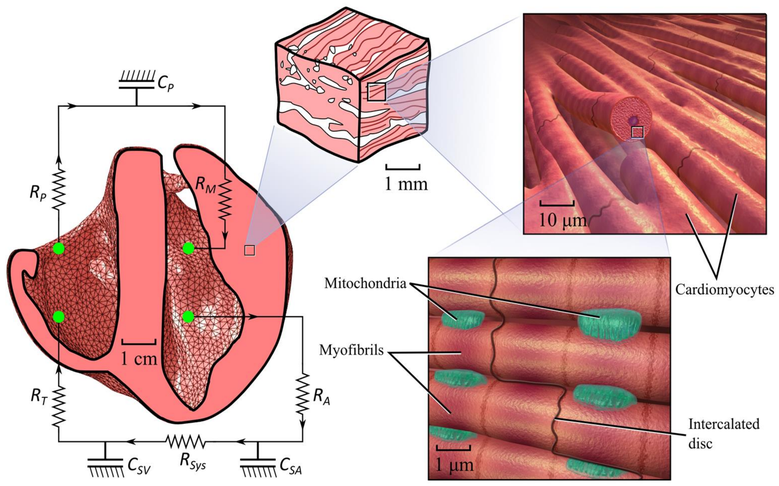

Figure 2: Schematic of the FE model of the healthy heart coupled to the lumped circulatory model. The constitutive model relies on linking macro behaviour to the underlying microstructure of the connected cardiomyocytes.

Calibration

Each model is calibrated using subject-specific *in vivo* recorded cardiac measurements for pressure and volume.

Validation

Independent tagged echocardiogram strain data on the endocardial surface were reserved for model validation. Agreement was excellent for the global circumferential strain (GCS) which was -22.0% (FEM) vs -21.9% (*in vivo*) for the healthy subject -14.4% (FEM) vs -12.7% (*in vivo*) for the HF subject. A regional analysis of comparison for FE model results reveals a very strong qualitative agreement between longitudinal and circumferential strains (Fig. 3).

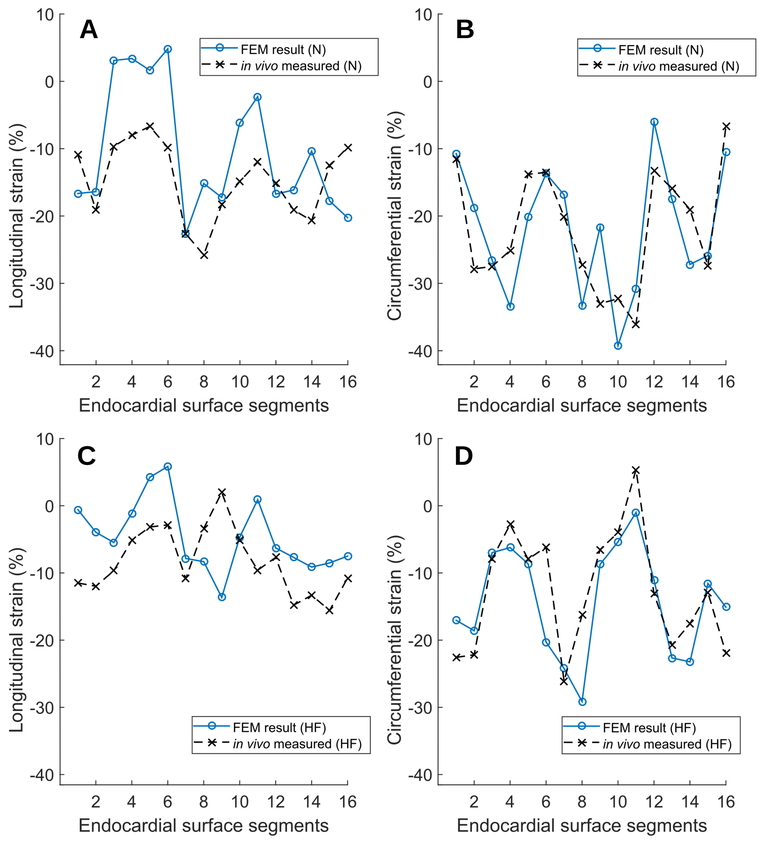

Figure 3: Longitudinal and circumferential endocardial strain comparison (16 regions) between the FE model (FEM) simulation and the in vivo recordings of the same subject. (A): Longitudinal strain results in the normal subject (N). (B): Circumferential strain results in the normal subject (N). (C): Longitudinal strain results in the heart failure subject (HF). (D): Circumferential strain results in the heart failure subject (HF).

Results

The mean volumetrically-averaged myofiber stress was found to have more than doubled in the left ventricle of the failing heart: 2.1 ± 4.2 kPa vs. 4.7 ± 4.9 kPa (healthy vs. failing) (Fig 4).

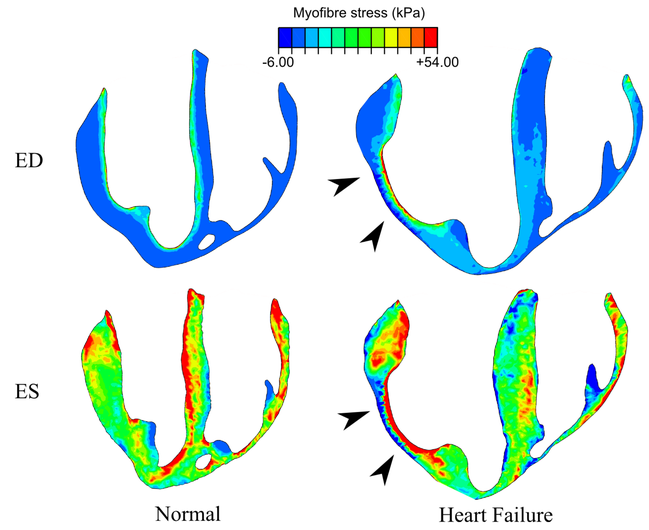

Figure 4: Myofiber stress at end-diastole (ED) and at end-systole (ES) for the normal (healthy) and diseased (heart failure) subjects. Infarcted/fibrotic region identified in the heart failure subject by black arrowheads.

These stresses were particularly high in the infarcted region, almost a magnitude of order higher as seen in the Table below.

LV myofiber stress (kPa)			
Time Point	Healthy tissue	Border-zone	Infarcted
ED	4.1 ± 4.5	4.6 ± 4.9	10.5 ± 10
ES	23.2 ± 19.8	24.1 ± 21.1	39.4 ± 43.8

Discussion and Conclusions

The high degree of subject-specificity incorporated into these models vastly reduces the number of model assumptions needed to produce computational cardiac simulations. This has led to our realistic determination of active tension (i.e., minimal cross-fiber contraction <15%) and the independently reached strain behavior, which matches the measured strains from *in vivo* echocardiography.

Subject specificity is introduced through geometric features, local myofiber directions, loading conditions, hemodynamics and the distribution of fibrotic tissue in the failing heart. The close global and regional agreement between *in vivo* and *in silico* strains illustrated the success of our methods to create computational models that can serve as *in silico* surrogates for real hearts in healthy and diseased states.

This level of agreement, and therefore validation, is a milestone for cardiac computational modeling. As such, stress and strain values presented in this study (for both ventricles and at multiple time points during the cardiac cycle) can serve as a guideline for future studies.

References

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2. Sack KL, et al. Partial LVAD restores ventricular outputs and normalizes LV but not RV stress distributions in the acutely failing heart in silico. *Int J Artif Organs* (2016) 39(8):421-30.